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Determination of surface properties and flow characteristics of salbutamol sulphate, before and after micronisation

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Abstract

Inverse gas chromatography (IGC) was employed to characterise the surface thermodynamic properties of two nominally equivalent batches of salbutamol sulphate and to highlight any surface energetic changes induced on micronisation. A powder flow avalanching analyser was used to probe the relationship between powder flow and the surface energetic properties. The results obtained demonstrate the potential of these techniques to detect and quantify differences in powder samples, before and after micronisation. They also indicate that surface energy differences detected by IGC can be related to important secondary processing properties such as powder flow. © 1998 Elsevier Science B.V. All rights reserved.

Keywords: Salbutamol sulphate; Inverse gas chromatography; Surface properties; Batch to batch variation; Acid–base interactions

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1. Introduction

The pressurised metered-dose inhaler (MDI) is the most frequently prescribed delivery system for inhaled treatments of asthma (Brindley et al., 1995). Whilst these systems will continue to be used with pharmaceutical companies working towards chlorofluorocarbon (CFC) free MDIs, alternative drug delivery systems are required. For this reason, multi-dose dry powder inhalers (MDPIs) are taking on an important role.

Batch-to-batch consistency and uniformity of raw materials for MDPIs is crucial if efficient processing and product performance are to be achieved and maintained. In the case of dry pow-

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der inhalers, the raw materials required are ultrafine, micronised drug particles (usually between 0.5 and 7.0μm to maximise their delivery and deposition in the lower respiratory tract) with or without larger sized inert powder carrier particles, typically α-lactose monohydrate (Ganderton and Kassem, 1992).

The complexity of particle formation and pretreatment operations means that minor differences in the preparation conditions from batch to batch can result in variations in the physical properties of routinely manufactured, supposedly equivalent, batches. At the moment many of these subtle batch-to-batch variations are unnoticed, remaining undetected by routine compendial and in-house testing. In fact, it is common experience for supposedly chemically equivalent materials to occasionally behave unpredictably and impair the development or manufacture of products (York, 1994). A strategy is therefore required which will highlight the limits of batch-to-batch variation which can be tolerated by a dry powder formulation without constraining the quality, efficacy and performance of the final product.

In addition, most materials used in pharmaceutical preparations are rarely crystallised at the required or optimum size and are therefore generally comminuted at some stage during their manufacture. This can cause varying and uncontrolled degrees of disruption to the crystallised structure. This disturbance, also called mechanical activation (Ahlneck, 1993), will rarely distribute uniformly throughout the powder mass, but most likely predominate at the surfaces which have interfaced with the processing stress, producing disordered and/or amorphous regions on the particle surfaces (Elamin et al., 1995). These variations can influence processing and formulation characteristics which may ultimately affect the quality and performance of the final product (Rowe et al., 1994).

As processing operations such as milling, blending and micronisation produce mechanical activation phenomenon, the traditional bulk measurement techniques such as differential scanning calorimetry (DSC), thermogravimetric analysis (TGA), powder X-ray diffraction (PXRD) and infra-red spectroscopy (IR) highlight some material differences but others remain undetected by

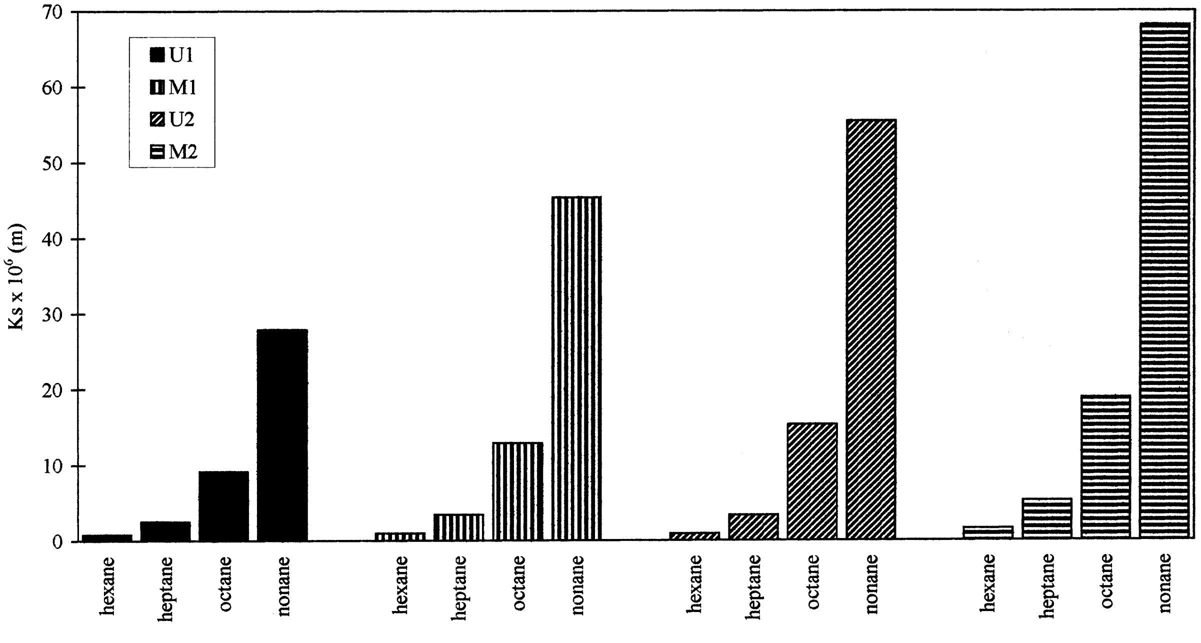

Fig. 1. Non-polar probe surface partition coefficients for U1, U2, M1 AND M2.

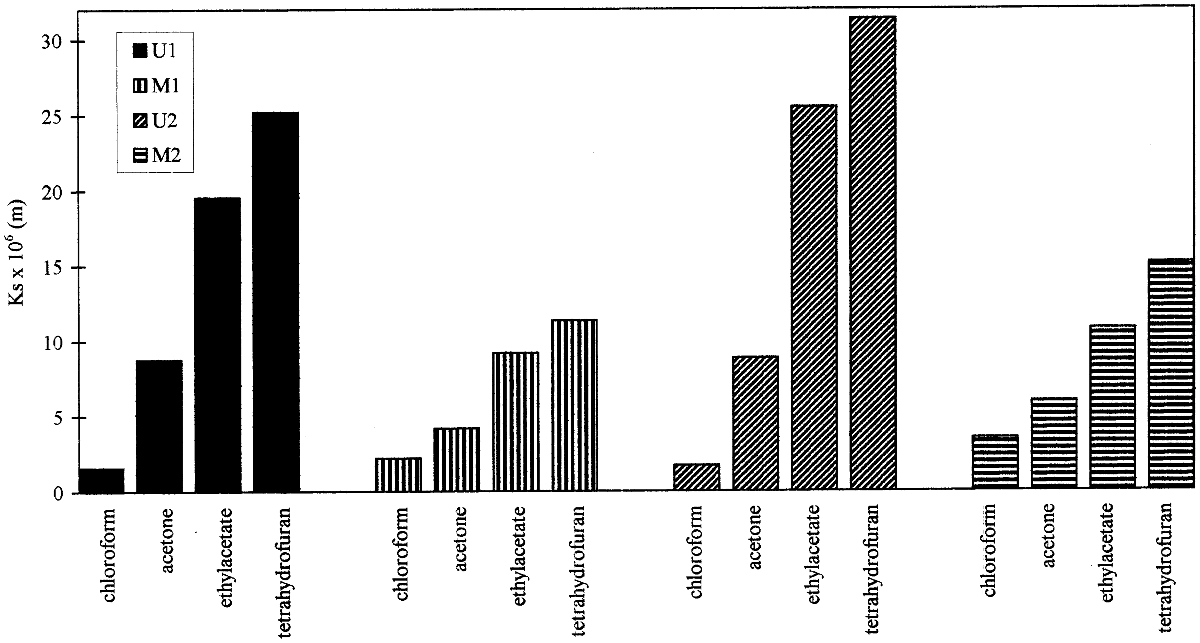

Fig. 2. Polar probe surface partition coefficients for U1, U2, M1 and M2.

Table 1

$-\Delta G_A$ values for batches U1, U2, M1 and M2 (standard deviation figures in brackets)

Probe	$-\Delta G_A$ (kJ/mol)			
	U1	M1	U2	M2
Hexane	83.18 (0.06)	83.86 (0.08)	83.58 (0.01)	85.09 (0.18)
Heptane	86.29 (0.17)	87.03 (0.15)	86.97 (0.03)	88.10 (0.15)
Octane	89.45 (0.21)	90.37 (0.17)	90.78 (0.22)	91.30 (0.17)
Nonane	92.28 (0.29)	93.54 (0.27)	94.01 (0.23)	94.54 (0.27)
Chloroform	85.03 (0.13)	85.95 (0.28)	85.28 (0.10)	87.09 (0.28)
Acetone	89.34 (0.30)	87.55 (0.18)	89.41 (0.01)	88.43 (0.18)
Ethylacetate	91.37 (0.43)	89.52 (0.30)	92.07 (0.16)	90.75 (0.30)
Tetrahydrofuran	92.01 (0.36)	89.57 (0.15)	92.59 (0.13)	89.89 (0.35)

the these testing methods (Ward and Schultz, 1995). Therefore, whilst intensive chemical screening should be routinely carried out, increased attention is required on other groups of powder properties such as surface chemical properties, surface crystallographic structure and surface thermodynamics.

In probing these surface properties the ideal techniques should be nondestructive to the surface, measure only the outermost layers of molecules and have a resolution down to very small surface areas. (Zografi, 1981) By using a combination of methods, subtle but significant changes in powder properties can be exposed. Such exposure would allow changes during processing and storage to be monitored and may even direct studies to modify the surface so as to alter its properties in a desired manner.

In this study inverse gas chromatography (IGC) was employed to detect and quantify differences in the surface thermodynamic properties of two supposedly equivalent batches of salbutamol sulphate and to provide insight into any surface energetic changes induced on micronisation. Additionally a powder flow avalanching analyser (AeroFlow) was used to probe relationships between powder flow and constituent particle surface properties.

2. Materials and methods

Two nominally equivalent batches of salbutamol sulphate, before (U1 and U2) and after micronisation (M1 and M2) were generously donated by GlaxoWellcome, Ware, UK.

IGC was undertaken on a Hewlett Packard 5880A Gas Chromatograph equipped with an integrator, autosampler and flame ionisation detector. Data were obtained by flowing nitrogen gas at 10 ml/min through a silanised glass column packed with a known weight of sample and injecting small amounts of a range of liquid probes with differing polarities. The retention times and volumes of these probes measured at infinite dilution or near zero surface coverage, where retention is independent of the quantity of probe injected, reveal fundamental chemical information about the sample surface, particularly the surface thermodynamic properties (Ticehurst et al., 1994, 1996).

The probes employed were hexane (BDH Laboratory Supplies), heptane (Sigma-Aldrich, St Louis, MO), octane (Aldrich), nonane (Aldrich), chloroform (Sigma-Aldrich), acetone (Sigma-Aldrich), ethylacetate (Sigma-Aldrich) and tetrahydrofuran (Rathburn Chemicals), all 99+% pure.

Dynamic powder flow assessment was carried out with the AeroFlow Powder Avalanching Analyser (API, Amherst, USA). This involves placing a known weight of powder into a transparent perspex drum. As the drum is rotated the powder bed is carried up until an unstable state is reached and an avalanche occurs. The interval times between the avalanches was detected by the projection of a white light source through the drum onto a photocell array (Kaye, 1996).

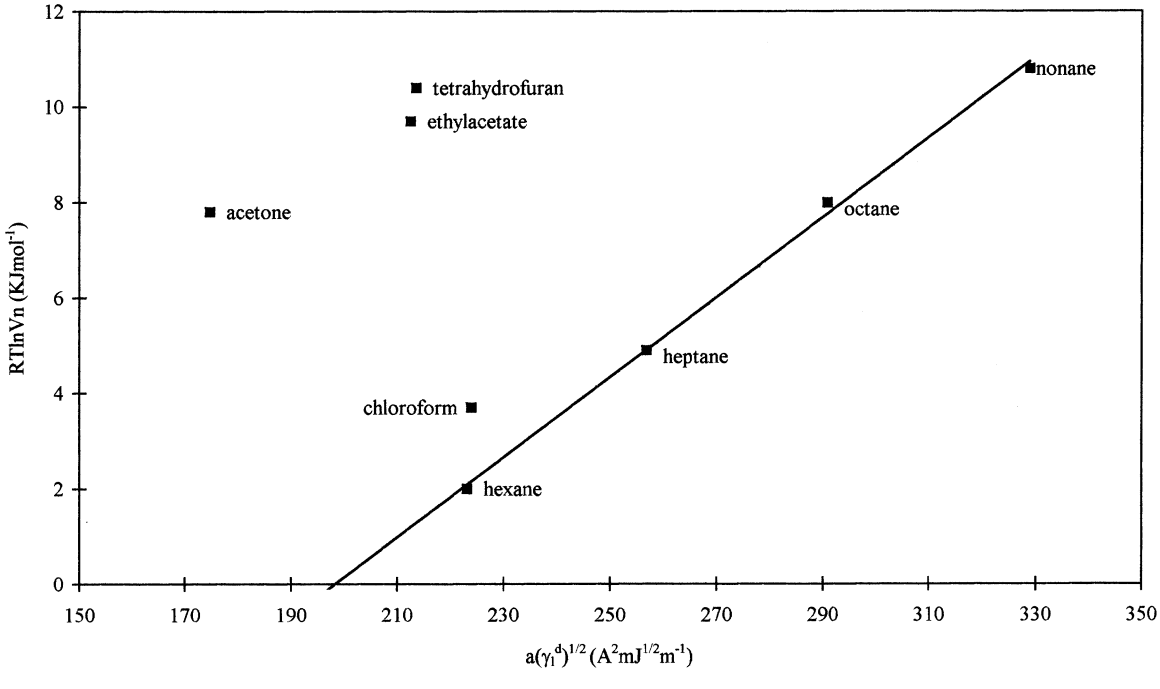

Fig. 3. Plot of RT ln V_n versus a$(\gamma_l^d)^{1/2}$ for the non-polar and polar probes of batch U1.

Table 2
γ_s^d and $-\Delta G_A^{SP}$ values for U1, U2, M1 and M2 (standard deviation figures in brackets)

Batch	γ_s^d (mNm^{-1})	$-\Delta G_A^{SP}$ (kJmol^{-1})							
		Chloroform		Acetone		Ethylacetate		Tetrahydrofuran	
U1	49.07	1.53	(0.12)	10.22	(0.25)	8.95	(0.28)	9.52	(0.30)
M1	58.57	1.98	(0.11)	8.19	(0.09)	5.13	(0.22)	6.58	(0.23)
U2	62.17	1.64	(0.09)	10.59	(0.14)	9.46	(0.19)	9.89	(0.17)
M2	64.54	2.03	(0.01)	7.70	(0.09)	6.83	(0.22)	6.55	(0.33)

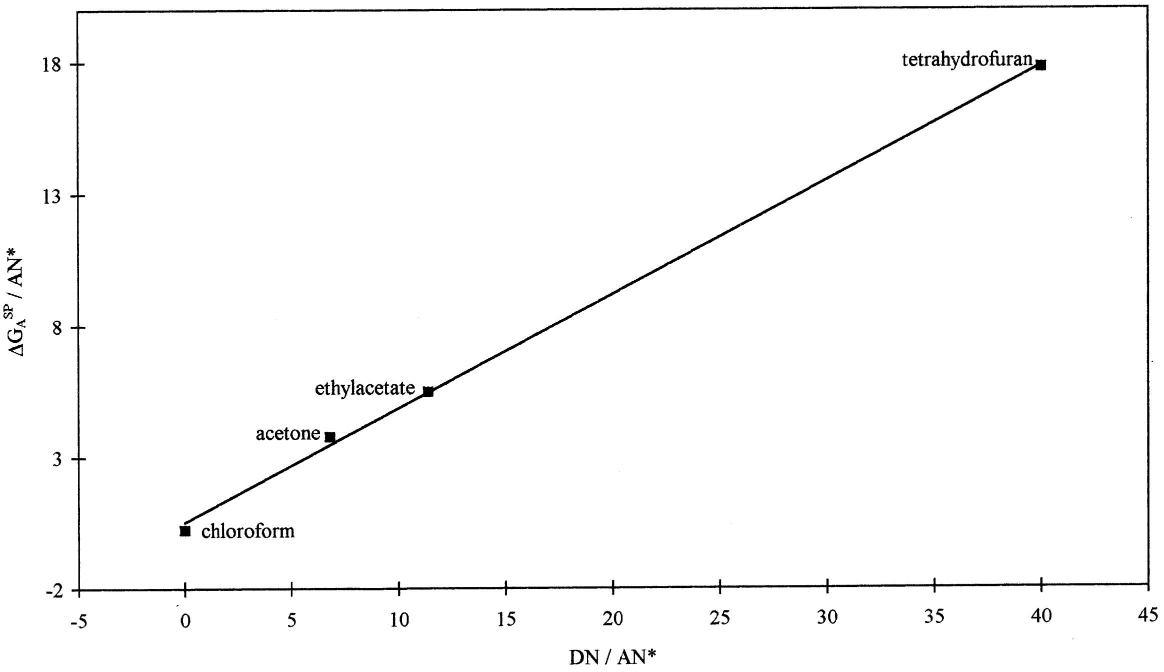

Fig. 4. Plot of $-\Delta G_A^{SP}/AN^*$ versus DN/AN^* for the polar probes of batch U1.

3. Results

3.1. Inverse gas chromatography

The primary experimental parameter measured in IGC is the net retention volume (V_n). V_n is related to the surface partition coefficient (K_s), defined as the ratio between the concentration of probe in the stationary phase and in the mobile phase, respectively.

$$K_s = V_n / m \cdot A_{sp} \quad (1)$$

where m is the weight of the sample in the column and Asp the specific surface area of the sample in the column. The surface partition coefficients for U1, U2, M1 and M2 for both the non-polar and polar probes are shown in Figs. 1 and 2, respectively.

From K_s the standard free energy of adsorption ($-\Delta G_A$) can be derived,

$$-\Delta G_A = \mathrm{RT}\ \ln(K_s \cdot P_{sg}/P) \quad (2)$$

where P_{sg} is the standard vapour state (101 KNm^{-2}) and P the standard surface pressure (0.338 mNm^{-1}). Calculated values of $-\Delta G_A$ for U1, U2, M1 and M2 for the various probes are listed in Table 1.

Table 3
K_A and K_D values for batches U1, U2, M1 and M2

Batch	K_A	K_D
U1	0.46	0.61
U2	0.48	0.70
M1	0.31	0.67
M2	0.28	0.99

Table 4
Mean avalanche times and irregularity of flow values for batches U1, U2, M1 and M2

Batch	Mean avalanche times	Irregularity of flow
U1	2.52	0.80
U2	2.65	0.84
M1	3.00	1.84
M2	3.89	2.24

Dispersive and specific interactions are considered to contribute independently to the adsorption of the probe molecules and represent the non-polar and polar properties, respectively, of the surface. Adsorption of non-polar probes (e.g. alkanes) results from dispersive interactions only, whereas polar probes are capable of both dispersive and specific acid–base interactions with the powder surface. Following the method of Schultz et al. (1987) who derived the equation:

$$RT \ln V_n = a(\gamma_l^d)^{1/2} 2N(\gamma_s^d)^{1/2} + C \qquad (3)$$

where N is Avogadro's number and γ_s^d the dispersive component of surface free energy of the solid sample, γ_s^d can be calculated from the gradient of the straight line produced by the alkanes. The specific component of the surface free energy of

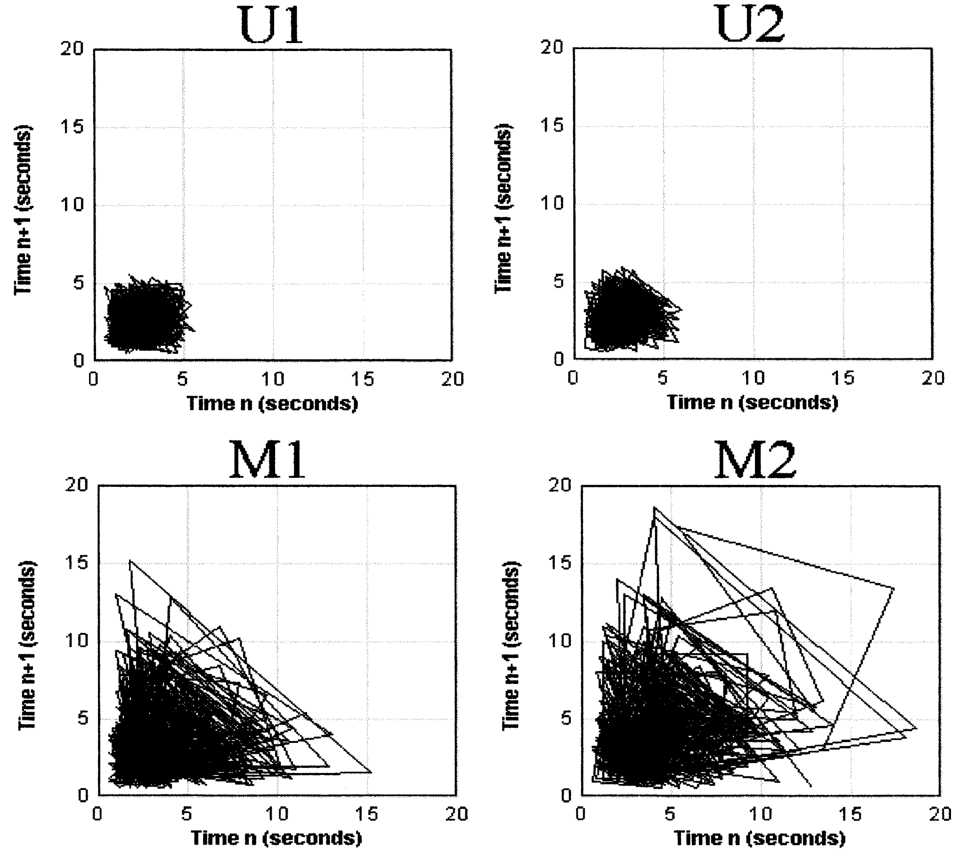

Fig. 5. Strange attractor plots for U1, U2, M1 and M2.

adsorption ($-\Delta G_A^{SP}$) is determined from the vertical distance between the alkane reference line and the polar probe of interest (see Fig. 3). Values of γ_s^d and $-\Delta G_A^{SP}$ are given in Table 2.

According to the theories developed by Drago et al. (1971) and Gutmann (1978) the specific interactions derived from IGC are essentially Lewis acid–base interactions or electron acceptor–donor interactions, enabling an estimate of the acid–base surface properties of the powders to be determined. The donor number (*DN*) defines the basicity or electron-donor ability of a probe whilst the acceptor number (*AN*) defines the acidity or electron-acceptor ability. More recently, Fowkes (1990) created a more suitable acceptor number (*AN**) correcting for a dispersive component contribution to *AN*.

From these numbers and the mean $-\Delta G_A^{SP}$ values determined by IGC the acid (K_A) and base (K_D) parameters of the powders can be calculated according to the equation:

$$-\Delta G_A^{SP} = K_A \cdot DN + K_D \cdot AN^* \quad (4)$$

Plotting $-\Delta G_A^{SP}/AN^*$ against DN/AN^* (see Fig. 4) produced a straight line with K_A and K_D evaluated, respectively, from the gradient and the intercept, with estimated values shown in Table 3.

3.2. AeroFlow powder avalanching analyser

Interval times between avalanches were plotted as discrete phase maps known as strange attractor plots (Kaye and Gratton-Liimatainen, 1995). Free flowing powders will produce strange attractor plots close to the origin with small spread, whilst in contrast cohesive powders give plots with a larger spread and a centroid positioned further from the origin. The strange attractor plots for U1, U2, M1 and M2 are shown in Fig. 5. Values of mean avalanche time and irregularity of flow, given in Table 4, enable quantification of the flowability of the powder bed.

4. Discussion

4.1. Inverse gas chromatography

Examination of K_s and $-\Delta G_A$ data for the two unprocessed samples demonstrates the more thermodynamically favourable adsorption of probes onto the surface of batch U2, compared to batch U1. The larger values for γ_s^d and $-\Delta G_A^{SP}$ also obtained for batch U2 indicate that constituent particle surfaces are more energetic in terms of both its dispersive and specific components of surface free energy, i.e. for both non-polar and polar surface interactions. From the specific interaction data both batches of unprocessed salbutamol sulphate appear amphoteric and able to function as electron donors and electron acceptors, although the basic or electron donor character appears to dominate. The larger K_A and K_D values obtained for batch U2 indicate that the surface of U2 is both a stronger electron donor and stronger electron acceptor than batch U1.

For the micronised batches, the increased values of K_s and $-\Delta G_A$ for the non-polar alkanes and the increase in γ_s^d imply that the surfaces of M1 and M2 have more energetic surfaces for non-polar, dispersive surface interactions than the unprocessed batches they were produced from. K_s, $-\Delta G_A$ and the specific interaction ($-\Delta G_A^{SP}$) for the acidic polar probe (chloroform) have also increased, but this is in contrast to the falls observed for the amphoteric (acetone) and basic (ethylacetate, tetrahydrofuran) polar probes. This suggests stronger basic or electron donor interactions at the surface of M1 and M2, which is supported by the observed increase in K_D and decrease in K_A. The micronised salbutamol sulphate remains amphoteric but relative basicity has increased, which may be the result of the exposure of more basic functional groups on a molecular scale at the particle surface after particle breakage on micronisation due to a preferred slip plane within the crystal lattice. This aspect is being investigated using a molecular modelling approach.

4.2. AeroFlow powder avalanching analyser

Examination of the strange attractor plots clearly shows visually the difference in flow between the unprocessed and micronised samples. Whilst smaller differences are observed between the two unprocessed and the two micronised materials.

U2 exhibits slightly poorer flow properties than U1, with more outlier avalanches. M2 has rogue avalanches reaching up to twenty seconds suggesting that this batch has poorer flow properties than M1. These observations are mirrored by the mean avalanche times and irregularity values in Table 4. Thus, the micronised sample with the most energetic surface as revealed by IGC has the poorest flow properties.

4.3. General conclusions

The results obtained demonstrate the potential of IGC and avalanching powder flow to detect and quantify differences in supposedly equivalent samples of powders, before and after processing, by micronisation. Analyses also indicate that surface energy differences detected by IGC can be related to important secondary processing properties such as powder flow. Thus subtle changes in surface energetic properties induced by pretreatment such as micronising, may lead to modified secondary processing behaviour with potential downstream and product performance consequences.

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References

Ahlneck, C., 1993. Chemical and physical stability of drugs in the solid state. Industrial Aspects of Pharmaceutics. Swedish Pharmaceutical Press, Stockholm, pp. 80–92.

Brindley, A., Sumby, B.S., Smith, I.J., Prime, D., Haywood, P.A., Grant, A.C., 1995. Design, manufacture and dose consistency of the serevent diskus inhaler. Pharm. Tech. Eur. 1, 14–22.

Drago, R.S., Vogel, G.C., Needham, T.E., 1971. A four-parameter equation for predicting enthalpies of adduct formation. J. Am. Chem. Soc. 93, 6014–6026.

Elamin, A.A., Sebhatu, T., Ahlneck, C., 1995. The use of amorphous model substances to study mechanically activated materials in the solid state. Int. J. Pharm. 119, 25–36.

Fowkes, F.M., 1990. Quantitative characterisation of the acid–base properties of solvents, polymers, and inorganic surfaces. J. Adhesion Sci. Technol. 4, 669–691.

Ganderton, D., Kassem, N.M., 1992. Advances in Pharmaceutical Sciences. Academic Press, London, UK, pp. 165–191.

Gutmann, V., 1978. The Donor–Acceptor Approach to Molecular Interactions. Plenum, New York.

Kaye, B.H., Gratton-Liimatainen, J., Faddis, N., 1995. Studying the avalanching behaviour of a powder in a rotating disc. Part. Part. Syst. Charact. 12, 197–201.

Kaye, B.H., 1996. Sampling and characterisation research: developing two tools for powder testing. Powder Bulk Eng. 1, 44–54.

Rowe, R.C., Parker, M.D., Bray, D., 1994. Batch and source variations in excipients-quantification using microcalorimetry. Pharm. Tech. Eur. 6, 26–30.

Schultz, J., Lavielle, L., Martin, B., 1987. The role of the interface in carbon fibre-epoxy composites. C. J. Adhesion 23, 45–60.

Ticehurst, M.D., Rowe, R.C., York, P., 1994. Determination of the surface properties of two batches of salbutamol sulphate by inverse gas chromatography. Int. J. Pharm. 111, 241–249.

Ticehurst, M.D., York, P., Rowe, R.C., Dwivedi, S.K., 1996. Characterisation of the surface properties of α-lactose monohydrate with inverse gas chromatography, used to detect batch variation. Int. J. Pharm. 141, 93–99.

Ward, G.H., Schultz, R.K., 1995. Process-induced crystallinity changes in albuterol sulfate and its effect on powder physical stability. Pharm. Res. 12, 773–779.

York, P., 1994. Powdered raw materials: Characterising batch uniformity. Respiratory Drug Delivery IV Conference, Richmond, USA, pp. 83–91.

Zografi, G., 1981. Interactions at the vapour solid interface in pharmaceutical systems. Topics in Pharmaceutical Sciences. Biomedical Press, Elsevier/North-Holland, pp. 427–442.